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"FLUOTHANE": A REPORT TO THE MEDICAL RESEARCH COUNCIL BY THE COMMITTEE ON NON-EXPLOSIVE ANAESTHETIC AGENTS*

The Committee on Non-explosive Anaesthetics was formed by the Medical Research Council to consider what steps can be taken to find anaesthetics the use of which is unattended by the risk of explosion. The best-known substances which can give rise to explosion are ether and cyclopropane. While it is true that the explosions they cause are rare, much time and money is spent in taking precautions to minimize the risk, in particular to prevent the accumulation of electrostatic charge on operating-theatre equipment.

The interest of the Committee has therefore been to encourage the synthesis of new compounds which will not explode and which are suited for use as anaesthetics, and to examine substances synthesized by commercial firms for this purpose. Recently "fluothane"† (halothane) has been prepared by Imperial Chemical Industries Ltd. (Pharmaceuticals Division), and reports on its properties and clinical use have been published (Raventós, 1956; Johnstone, 1956; Bryce-Smith and O'Brien, 1956). Chemically it is a derivative of ethane, in which three of the hydrogen atoms have been substituted by fluorine, a fourth has been substituted by bromine, and a fifth by chlorine. Fluothane probably owes its non-explosive character to the presence of the three fluorine atoms and to the reduction of the number of hydrogen atoms to one.

The following report describes investigations into the properties of fluothane, both pharmacological and clinical, in order to clarify some points in its pharmacology and to further its clinical assessment.

SOME PHARMACOLOGICAL ACTIONS OF FLUOTHANE

by PROFESSOR J. H. BURN, DR. H. G. EPSTEIN, DR. G. A. FEIGEN,‡ and PROFESSOR W. D. M. PATON

In the first pharmacological studies of fluothane, by Raventós (1956), it was established that this vapour could produce a rapid, effective, and flexible anaesthesia. It appears to possess, however, some unusual features when compared with other anaesthetics. First, it has a distinct hypotensive action. Raventós made the suggestion that this was due to ganglion block by fluothane, although it was necessary to postulate that such block was particularly effective on the mesenteric ganglia, since it was found that the superior cervical ganglion was not very readily paralysed. He did not think that fluothane appreciably depressed the cardiac output by weakening the cardiac muscle. Secondly, the effects of the anaesthetic appeared to pass off rapidly, and this recovery depended little on the duration of exposure. This is a particularly interesting point, in view of the high oil/water partition coefficient of fluothane. It is greater than that of chloroform, from which it might be expected that after prolonged administration a good deal of fluothane would be absorbed by fatty tissues and would take a considerable time to be eliminated.

In the following experiments (1) the effect of fluothane on the cardiac output has been studied; (2) the extent to which the fall in blood pressure could be attributed to ganglion block has been analysed further; (3) since fluothane undoubtedly possesses some ability to paralyse ganglia, a test of its actions on another cholinergic synapse, the neuromuscular junction, has also been made; (4) finally, evidence about the time course of its actions has been obtained.

Methods

For experiments on cardiac output, the dog heart–lung preparation was set up, ventilated by a Starling respiration pump. The experiments were made with constant venous pressures, usually 6 cm. of water, in some experiments at 11 and 15 cm. of water also. The pressure in the artificial resistance was adjusted to about 130 mm. of mercury and the venous inflow regulated to permit a systemic output of 800–1,200 ml. a minute at a venous pressure of 6 cm. of water. The outflow was measured directly by diverting the blood on its way to the venous reservoir and recording the outflow for a period of 15 seconds. When a series of observations showed that heart rate and output were constant, a change was made from the pump inflating the lungs with air to a pump giving a known concentration of anaesthetic. The output was measured at intervals of one minute for 10 to 25 minutes. Ventilation with air was then resumed and continued until the output had recovered its original value or until it had become steady at a lower figure. The procedure was then repeated with a different concentration of fluothane or of some other anaesthetic.

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†The name "fluothane" is the trade mark of Imperial Chemical Industries Ltd. (Pharmaceuticals Division) and is used throughout the report to describe their brand of trifluorochlorobromoethane (halothane). The Committee wishes to express its thanks to the company for the generous assistance they have given and for providing the fluothane used for this trial.

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For the experiments on autonomic ganglia, the blood pressure, the neuromuscular junction, and the knee-jerk, cats anaesthetized with chloralose after induction with ethyl chloride and ether were used. Records were made of the contraction of the nictitating membrane (after enucleation of the eyeball) in response to maximal stimulation at 10 per second of the cervical sympathetic, separated from the vagus nerve and cut centrally. In some experiments the peripheral stump of the vagus, cut in the neck, was stimulated and the effect on the heart rate recorded. The blood pressure was recorded through a cannula in a carotid artery. In the study of neuromuscular actions, the response of the soleus and tibialis muscles, recorded by means of flat spring myographs, in response to maximal shocks applied to the sciatic nerve was used. The knee-jerk was elicited by a solenoid tapping the quadriceps tendon and recorded by means of a thread attached to the ankle moving a lever writing on the smoked drum.

To obtain known concentrations of fluothane, modified E.M.O. inhalers calibrated for fluothane were used. The same inhalers were also calibrated for trichlorethylene (" trilene ") and chloroform, and for experiments with ether an Oxford vaporizer was used. In the experiments on the dog heart–lung, a stroke volume of 150 ml. and a rate of 26 a minute were usually employed ; in the experiments on the cat a stroke volume of 50 ml. and a rate of 19–20 a minute were used. The inhalers were immersed in a water-bath at about 27° C. to stabilize their temperatures.

Effect of Fluothane on Cardiac Output

Table I shows the effect of fluothane at various concentrations on four preparations. Fig. 1 A shows the mean results plotted, giving the reduction in cardiac output against the duration of exposure for five different concentrations of fluothane. From these lines can be estimated the time required for each concentration to reduce the output by 30% of the initial value. If the logarithm of the reciprocal of this time is plotted against the concentration of fluothane an approximately linear relationship is obtained (Fig. 2).

TABLE I.—*Effect of Fluothane on Systemic Output*

Exp.	Concentration of Fluothane	Output (ml./15 sec.)			Time of Admin. (min.)	Venous Pressure (mm. Water)	% Fall
		Control Before	Control After	During Fluothane			
1	1%	243	221	191	24	60–69	17·6
	2%	217	192	110	7·5	60–69	46·0
2	1·5%	220	203	173	10	60–65	18·2
3	1·2%	290	274	260	13	65	7·8
		242	230	224	15·5	60	5·1
4	1·2%	300	276	220	11·25	69	23·6
		196	200	162	13·25	60	18·1
	1·7%	240	242	148	10·5	69	38·6
		182	176	84	13	60	53·0

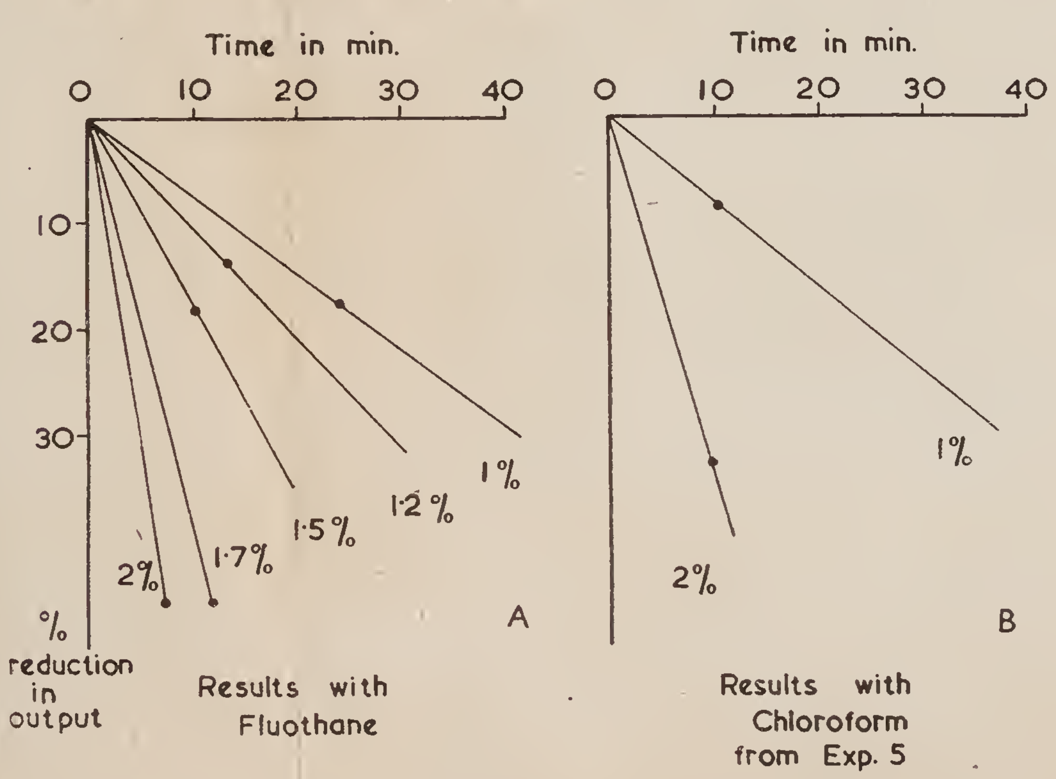

FIG. 1.—A, The effect of different concentrations of fluothane on the cardiac output in the heart–lung preparation of the dog. B, Similar results with chloroform.

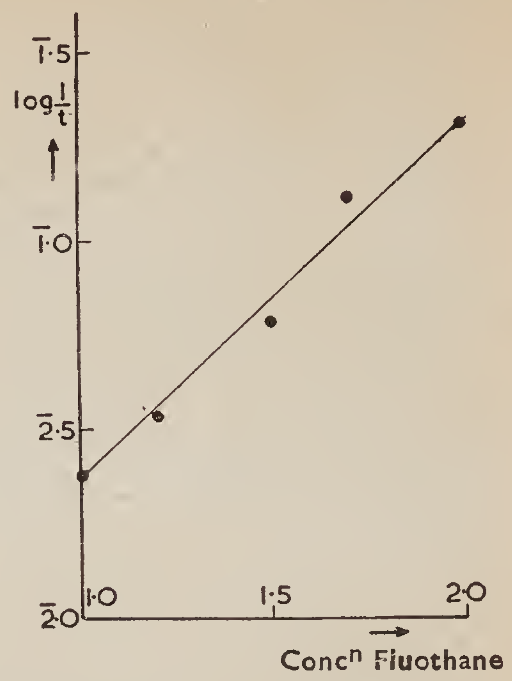

FIG. 2.—The reduction in cardiac output is proportional to the concentration of fluothane. The ordinate is the logarithm of the reciprocal of the time taken to reduce the output by 30%.

Experiments on Chloroform, Ether, and Trichlorethylene

Similar observations with chloroform were made (Table II) and the results in Experiment 5 are shown in Fig. 1B. In Experiment 4 a direct comparison with fluothane was made (Table III). This comparison indicated that 1.7% fluothane produced the same fall in output as 1.2% chloroform ; thus fluothane had about 70% of the action of chloroform in diminishing cardiac output.

With ether in concentrations up to 10% only small changes in output were obtained (Table IV). Similarly with trichlorethylene in concentrations up to 2% only small changes were seen (Table V).

TABLE II.—*Effect of Chloroform on Systemic Output*

Exp.	Concentration of Chloroform	Output (ml./15 sec.)			Time of Admin. (min.)	Venous Pressure (mm. Water)	% Fall
		Control Before	Control After	During Chloroform			
5	1%	223	224	206	10·25	60	8·4
	2%	224	224	150	9·75	60	33·0
4	1·2%	232	211	128	10·75	60–69	42·0

TABLE III.—*Comparison of Fluothane and Chloroform in Experiment* 4

	Time of Action	% Fall in Output
Fluothane 1·2%	5·75 min.	8·5
	10·75 ,,	18·7
Chloroform 1·2%	5·75 ,,	20·8
	10·75 ,,	42·0
Fluothane 1·7%	5·5 ,,	23·4
	10·5 ,,	40·2

TABLE IV.—*Effects of Ether on Systemic Output*

Exp.	Concentration of Ether	Output (ml./15 sec.)			Time of Admin. (min.)	Venous Pressure (mm. Water)	% Fall
		Control Before	Control After	During Ether			
2	6·0%	203	189	176	10	60–65	10·2
6	4·0%	222	214	222	15	60	—
	8·0%	222	214	214	16	60	4·0
7	5·0%	253	253	247	9·75	60	2·4
	10·0%	253	253	242	10·5	60	4·3

TABLE V.—*Effects of Trichlorethylene on Systemic Output*

Exp.	Concentration of Trichlorethylene	Output (ml./15 sec.)			Time of Admin. (min.)	Venous Pressure (mm. Water)	% Fall
		Control Before	Control After	During Trichlorethylene			
3	1·5%	248	247	242	5·75	60–65	2·2
		248	247	244	11·0	60–65	1·4
6	1·0%	214	—	206	9·25	60	3·5
	2·0%	156	150	150	16·0	60	2·0
7	1·0%	252	252	249	10·5	60	1·2
	2·0%	252	240	234	9·5	60	4·8

Effects on Heart Rate

The heart–lung preparation does not receive impulses from the central nervous system, so that the heart rate depends only on the pacemaker. Fluothane, 1–2%, had little effect on the rate; thus a concentration of 1% caused the rate to rise from 150 to 160 a minute, and at 2% the rate fell again to 148, where it remained when ventilation with air was resumed.

Chloroform 1% had little effect, but 2% raised the rate from 150 to 179. The rate returned to 150 on air.

Ether accelerated the heart distinctly. Thus a concentration of 5% raised the rate from 114 to 133, and 10% produced a further rise to 145 a minute.

Trichlorethylene had the greatest effect on the rate; with a concentration of 1% the rate increased from 148 to 174 in one experiment and from 133 to 142 in another. In two experiments a concentration of 2% raised the rate from normal values of 148 and 133 to 213 and 160 a minute respectively.

In the cat under chloralose, fluothane has little effect on the heart rate; there may be a slight slowing of the heart—for example, from 172 to 160 beats a minute. Atropine (0.1 mg./kg.) does not cause any significant cardio-acceleration, if given during the fluothane administration; nor does it antagonize the fall in blood pressure produced by fluothane (discussed below).

Hypotensive Action of Fluothane in Relation to Ganglion Block

Fig. 3 shows a comparison of the effect of 2.65% fluothane on the systemic blood pressure and on the response of the nictitating membrane to sustained preganglionic excitation. It will be seen that, despite the fall in blood pressure from 118 to 52 mm., the action on ganglionic transmission is rather small. In the same figure (Fig. 3 B) is shown a later test of the effect of hexamethonium, when it can be seen that even a large dose of hexamethonium fails to lower the blood pressure so far, whereas a dose of hexamethonium producing a distinct depression of transmission in the ganglion has a rather slight effect on the blood pressure. The discrepancy between the intensity of ganglion block and the hypotensive action produced by fluothane is a large one, sufficient to make it doubtful whether ganglion block could account for the fall. The suggestion has been made that the vasomotor ganglia in the visceral area are particularly sensitive to ganglion block by fluothane. It was found, however, that if the animal was eviscerated a vigorous fall in blood pressure could be produced (Fig. 4). despite the absence of the circulation in the alimentary tract and liver.

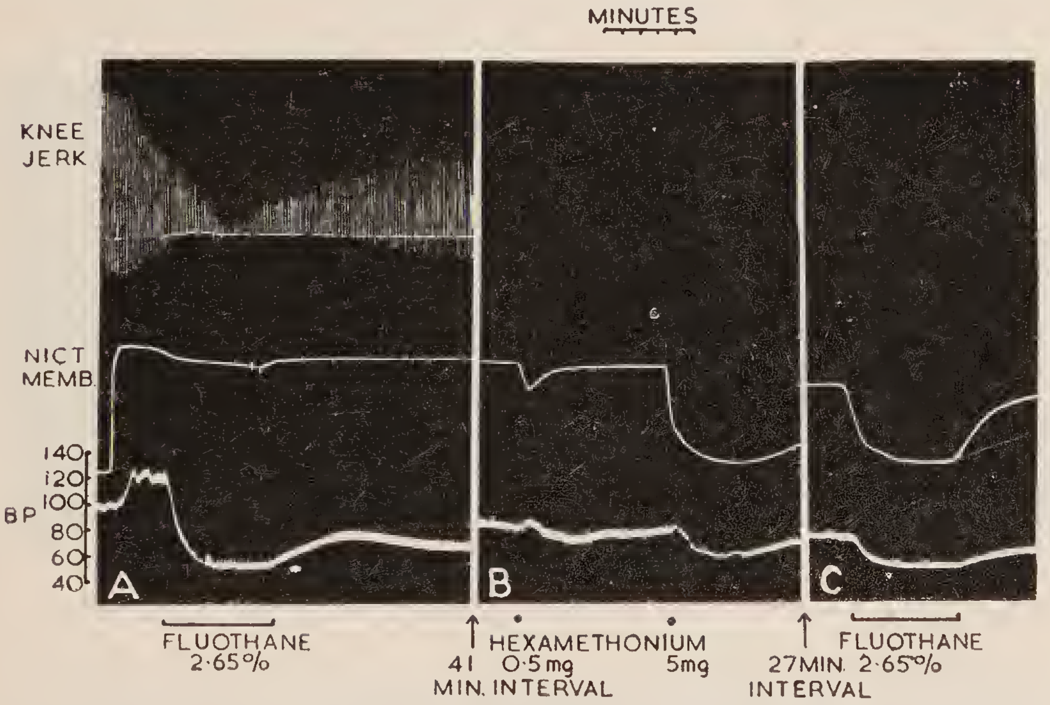

FIG. 3.—Records of the knee-jerk (upper tracing), contraction of the nictitating membrane (middle tracing), and blood pressure (lower tracing) in a cat under chloralose. A, Effect of fluothane 2.65%, showing large effect on knee-jerk and blood-pressure and small effect on ganglion transmission. B, Effect of hexamethonium, injected intravenously: first 0.5 mg., then 5 mg., showing greater effect on ganglion transmission than on blood pressure. C, Effect of fluothane inhalation when recovery from hexamethonium not quite complete; ganglion block by fluothane is intensified.

A test was also made on the effects of fluothane on the response of the heart to vagal stimulation, which is mediated through the parasympathetic cardiac ganglia. It was found that, even after a profound fall in blood pressure, vagal action could still be obtained (Fig. 5). Indeed, the experiment was difficult, since the vagal action was sufficiently intense, despite the greatly lowered blood pressure, to threaten the survival of the animal. The contrast with hexamethonium is again striking, since with a dose of the latter of comparable or lesser hypotensive action the vagus effect is almost abolished and sometimes consists chiefly of a cardiac acceleration.

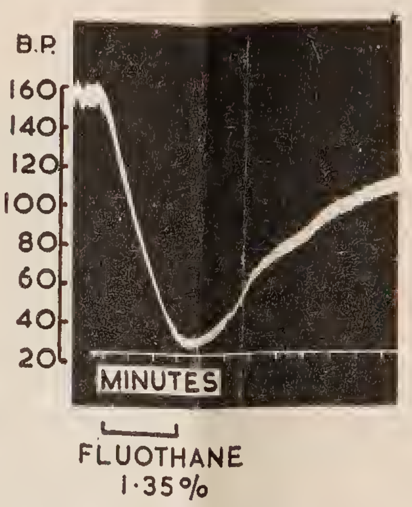

FIG. 4.—Record of the action of fluothane 1.35% on the blood pressure of a cat under chloralose and eviscerated.

It is clear, on the other hand, that fluothane can weaken ganglionic transmission (Fig. 3 A), even if this can hardly account for all its hypotensive actions. The aspect of this which may be of most practical importance is that of synergism with the action of a ganglionic blocking agent. Thus a dose of hexamethonium exerts a bigger effect in the presence of fluothane. This phenomenon is also seen with D-tubocurarine (Fig. 6). Conversely, if there is some

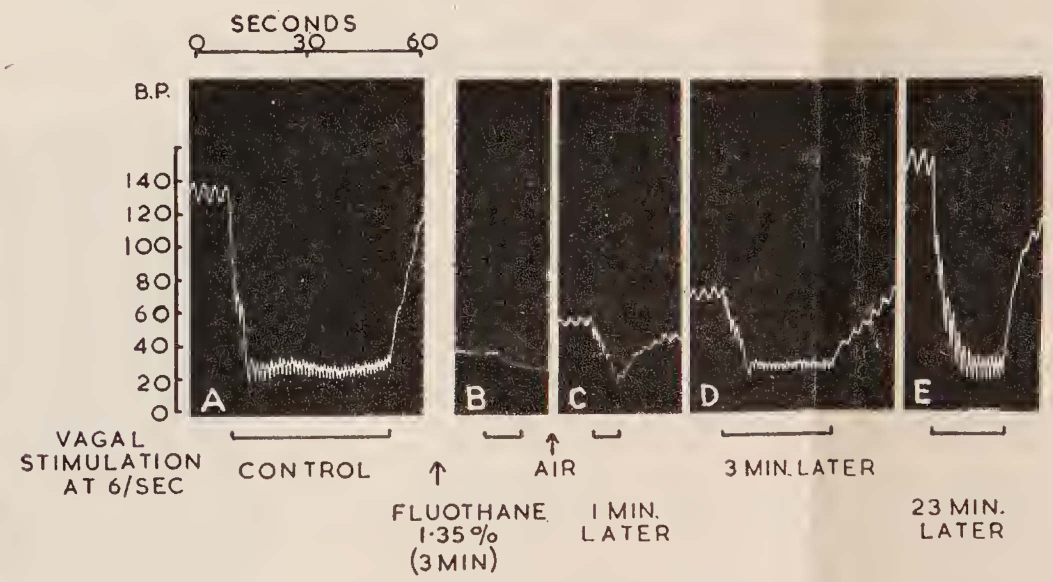

FIG. 5.—Record of the effect of vagal stimulation on the blood pressure of a cat under chloralose: A, normally; B, during inhalation of fluothane 1.35%; C, D, and E, during recovery from fluothane. The fluctuations of blood pressure before and after vagal stimulation are respiratory, the pulse rate being too fast (about 140 a minute) to show; but *during* vagal stimulation with the accompanying bradycardia individual heart beats are seen.

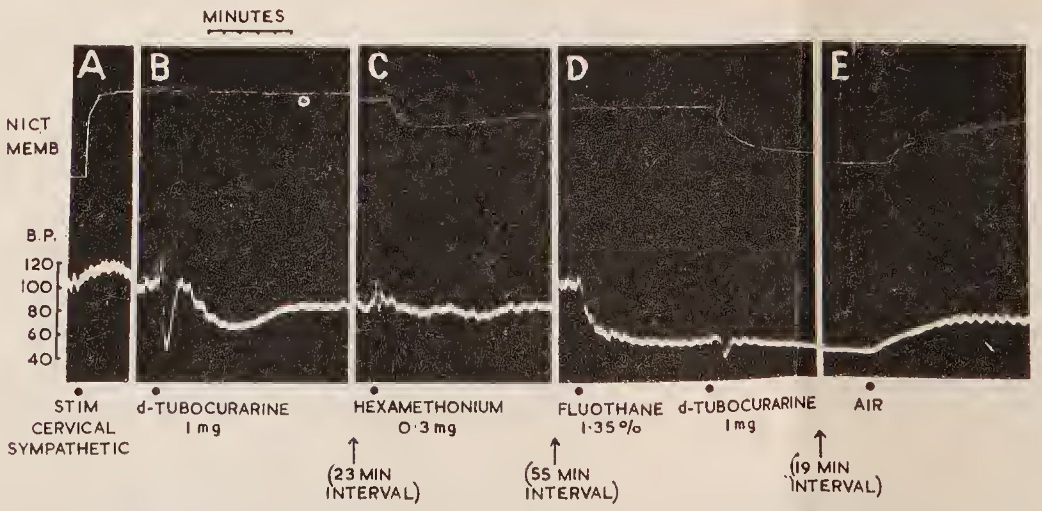

FIG. 6.—Record of blood pressure (lower tracing) and of contraction of nictitating membrane to continuous stimulation of the cervical sympathetic at 10 shocks a second (upper tracing) in a cat under chloralose. A, Start of sympathetic stimulation. B, D-Tubocurarine 1 mg. intravenously: no effect on ganglion transmission. C, Hexamethonium, 0.3 mg., producing moderate ganglion block. D, Fluothane inhalation produces a substantial fall of blood pressure, but no blocking action on the cervical sympathetic. D-Tubocurarine now, however, produces a deep paralysis of ganglion transmission. E, Return to breathing air. Reduction of blood pressure, and ganglion block, persist until fluothane inhalation ceases.

hexamethonium still remaining in the body, despite a nearly completed recovery of ganglionic transmission, administration of fluothane now has a much stronger ganglion-blocking action (Fig. 3 C).

It was concluded, therefore, that the ganglion-blocking action of fluothane could not account for its hypotensive effect, and that some other explanation should be sought for it.

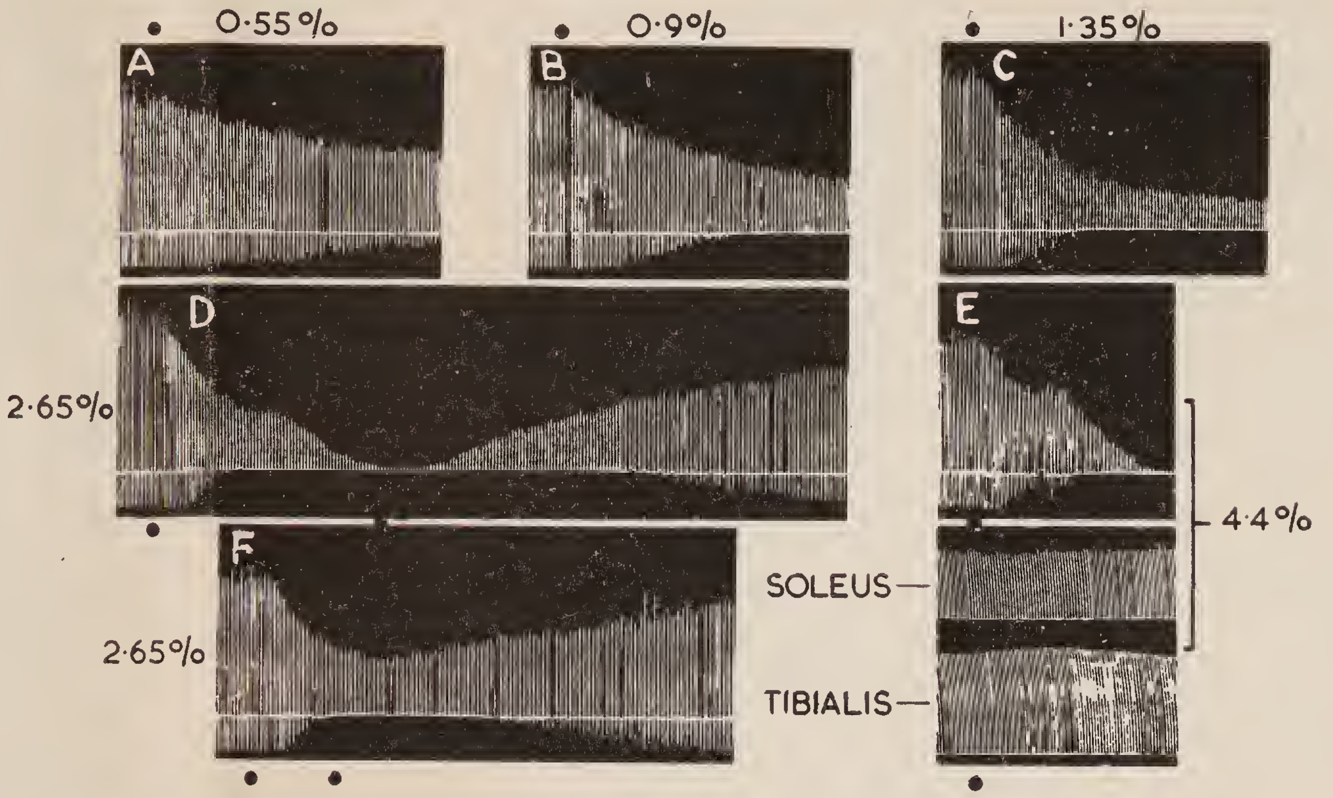

Fig. 7.—Effect of fluothane inhalation in various concentrations on the knee-jerk of one leg (A–F) and on the contraction of the soleus and tibialis muscles of the opposite leg excited by single maximal shocks to the sciatic nerve every 10 seconds, in the cat under chloralose. A–E, Increasing speed of paralysis of the knee-jerk with increasing concentrations of fluothane. E (lower part), The highest concentration of fluothane tested (4.4%) failed to reduce the indirectly excited tibialis or soleus twitch. D–F, Comparison of the rates of recovery from fluothane 2.65% inhaled for different periods (shown by the black dots below the tracings). Recovery is longer the further the reduction of the knee-jerk is carried.

Action of Fluothane on Knee-jerk

The cat deeply anaesthetized with fluothane presents a blood-pressure record strikingly like that of a spinal animal; this suggested that the fall in blood pressure might be due to an action on the central nervous system. To obtain evidence in this direction, records of the knee-jerk (which is vigorous in the animal under chloralose) were obtained. It was found that all concentrations of fluothane tested (from 0.5% upwards) depressed the knee-jerk considerably, and a concentration of 1% abolished it (Fig. 7). The intensity of this action corresponded much more closely to the effects on the blood pressure than did the ganglionic action (Fig. 3).

These experiments also threw light on the duration of action of the drug. It was found that recovery was not in fact always of the same duration, and that the longer the exposure or the deeper the anaesthesia, the longer it took for the knee-jerk to return. On the other hand, if equal depressions of the knee-jerk were produced in different ways, the recovery times were comparable. It is difficult to make a corresponding assessment of recovery time on blood pressure, since this is apt to change during the course of an experiment in the absence of any treatment. But if the records in Fig. 3 and Fig. 8 are examined, it is clear that, despite an initially rapid component in return of blood pressure, there is a much more prolonged slower component whose duration corresponds tolerably well with that of the return of the knee-jerk.

The evidence is therefore compatible with the idea that fluothane exercises a centrally depressant action, and that the central autonomic paralysis resulting is a principal cause of the hypotension which fluothane induces. Fluothane, on this view, contrasts with other anaesthetics which lead to excitation of autonomic centres.

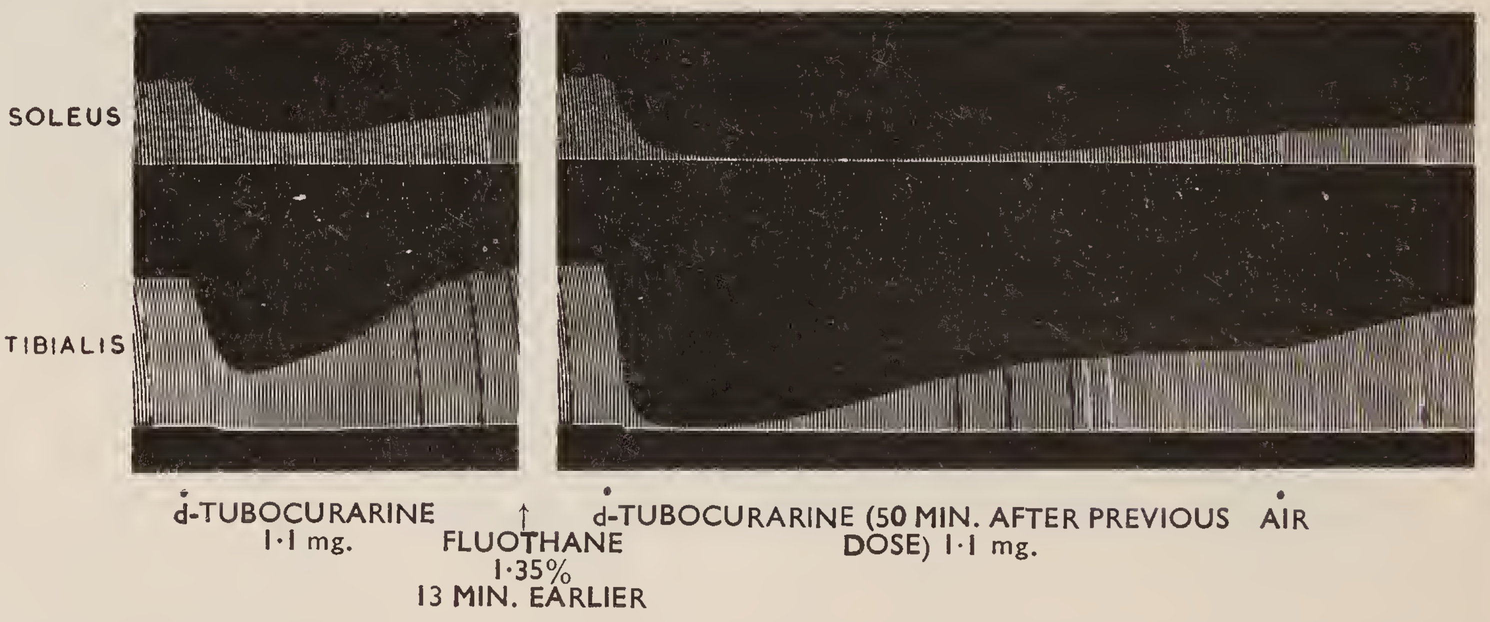

Fig. 9.—Record of the contractions of the soleus and tibialis to single maximal shocks to the sciatic nerve every 10 seconds, in a cat under chloralose. Thirteen minutes before the second panel, fluothane inhalation began. D-Tubocurarine, 1.1 mg. intravenously, has a deeper and more prolonged effect during fluothane inhalation. Return to breathing air accelerates recovery from the neuromuscular block.

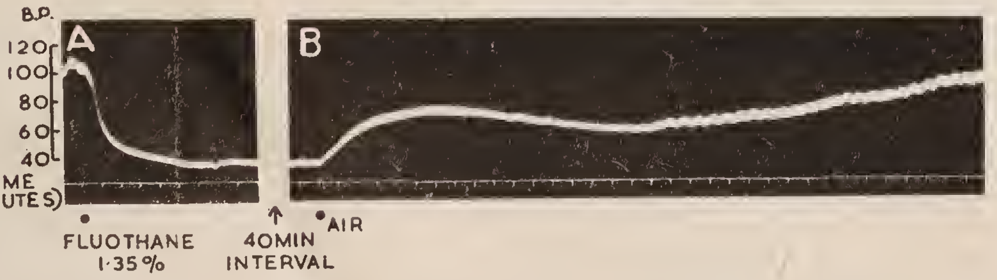

Fig. 8.—Record of blood pressure under chloralose. A, Effect of beginning fluothane inhalation. B, 40 minutes later, return to breathing air, showing initial partial rapid recovery followed by slower recovery phase.

Action of Fluothane on Neuromuscular Junction

The highest concentration of fluothane tested (4.4%) failed to reduce the twitch of either the tibialis or soleus muscle; indeed, a slight increment in twitch tension was sometimes seen, perhaps related to change in blood flow. If, however, a comparison was made of the actions of muscle relaxants in the presence or absence of fluothane, a neuromuscular effect could be demonstrated. D-Tubocurarine was distinctly potentiated, and suxamethonium (succinylcholine) was distinctly antagonized by fluothane 1.35% (Figs. 9 and 10). These effects correspond satisfactorily with the idea that fluothane has a feeble antagonism to

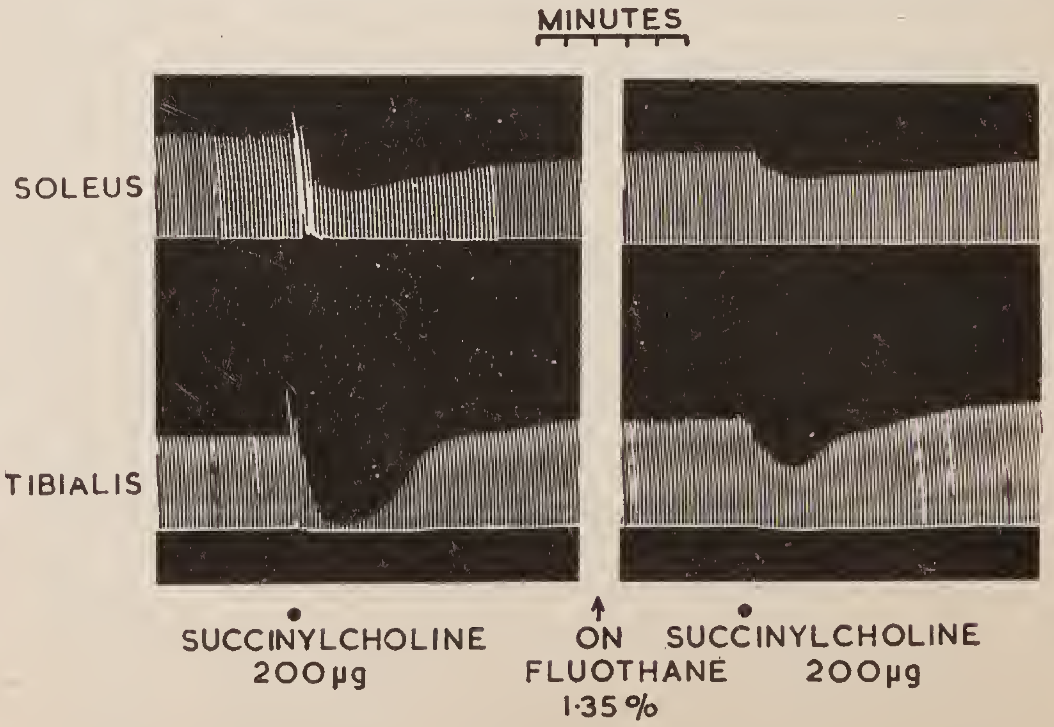

Fig. 10.—A similar experiment in another animal to that shown in Fig. 9, showing a reduction in the neuromuscular block produced by suxamethonium (succinylcholine), 200 µg. intravenously, if fluothane is inhaled.

acetylcholine (or other end-plate depolarizing drugs, such as suxamethonium) at the neuromuscular synapse, corresponding to its feeble antagonism at a ganglionic synapse. It may be, however, that some of the augmentation of D-tubocurarine's action may be related to the circulatory effect of the drug; for if the blood pressure is lowered enough the elimination of D-tubocurarine might be interfered with, leading to a more prolonged effect. The potentiation of D-tubocurarine by fluothane suggests that, in the event of a prolonged action by the relaxant, care should be taken to ensure the elimination of fluothane. Fig. 9 illustrates this point; the effect of D-tubocurarine persisted until fluothane anaesthesia was stopped and only then began to regress.

Discussion

These experiments show that the hypotensive action of fluothane is more complex than had been suggested. On the one hand, it is clear that fluothane in concentrations between 1 and 2% has a distinct depressant effect on the myocardium. Even though it is difficult to say precisely how great this action will be in the human, it is necessary, in the light of this evidence, to assume that in some degree it will also be present in clinical practice. On the other hand, it has been found that the ganglionic action of fluothane is hardly sufficient to account for the reduction of blood pressure it causes in the cat. It can produce a marked fall in the presence of a trivial action on the superior cervical ganglion; this fall is just as great in the eviscerated animal in which the mesenteric ganglia and splanchnic vascular bed can no longer influence the blood pressure. During the hypotension, vagal stimulation is still effective, although ganglionic block by hexamethonium, producing a smaller fall in blood pressure, may block the vagus much more intensely.

The experiments on the cat suggested, further, that another mechanism might be involved, that of a central depression of vasomotor mechanisms. Such an effect would be compatible with the reduction of the response to carotid occlusion described by Raventós. Evidence was obtained that fluothane in concentrations comparable to those exerting a hypotensive effect could depress a central nervous reflex, the knee-jerk; and that the magnitude and time course of this action correspond tolerably well with that on the blood pressure. It seems best, therefore, to suppose for the present that the hypotensive action of fluothane is made up of a central depressant action, together with some weakening of the heart, and possibly a small contribution of peripheral ganglion block.

There is, however, a distinct action by fluothane on autonomic ganglia. The most important practical aspect of this may be potentiation of ganglion-blocking agents if these are also administered. The ganglionic action of D-tubocurarine, as well as that of hexamethonium, is augmented. Corresponding to this depressant action at the ganglionic synapse is a similar action on the neuromuscular junction. Fluothane in a concentration up to 4.5% did not itself block transmission in either the tibialis or soleus muscles; but at 1.5% it was able to antagonize suxamethonium slightly and to potentiate D-tubocurarine markedly.

The preservation of vagal action in the presence of fluothane is an important feature of the anaesthetic, particularly in man, in whom a distinct bradycardia commonly occurs. Although it seems clear that the bradycardia in man is mediated, on the efferent side, by the vagus, its origin is still obscure and deserves further study. The preservation and (in man) activation of the vagal pathway means that effective atropinization may be particularly important with fluothane, especially if a drug such as neostigmine is to be given to accelerate recovery from a muscle relaxant. Among muscle relaxants, gallamine may prove to have a special place in fluothane anaesthesia, for Riker and Wescoe (1951) showed that it had a rather specific action in paralysing the ability of the vagus to slow the heart. This action is produced by ordinary dosage. Gallamine is virtually devoid of ganglion-blocking action, and one would anticipate such ganglion block by gallamine to be negligible even after potentiation by fluothane.

Finally, observations were made on the rate of recovery from fluothane. With the blood pressure there is, typically, a fairly rapid partial recovery sometimes followed by a subsequent depression, and then a second much slower phase of recovery. The knee-jerk, however, does not show this diphasic response but recovers more or less steadily, in parallel with the slower phase of return of blood pressure. The duration of recovery depends both on duration of exposure and on the depth of anaesthesia. Thus, after a prolonged or deep exposure it might require up to an hour before blood pressure and knee-jerk could be regarded as normal.

Summary

Fluothane reduces cardiac output in the dog heart–lung preparation. It is about 70% as active as chloroform in this respect.

Fluothane lowers the blood pressure, in the cat under chloralose, more than can be readily accounted for by ganglion block. It is equally active in the animal in which the splanchnic vascular bed is removed by evisceration.

Fluothane depresses the knee-jerk of the cat under chloralose in concentrations from 0.5% upwards. The intensity of this depression, together with its time course, corresponds sufficiently with that of the hypotensive action to suggest that the latter is produced by depression of central vasomotor mechanisms.

Fluothane, though not itself strongly ganglion-blocking, potentiates ganglion block by hexamethonium and D-tubocurarine.

Fluothane up to 4.5% does not paralyse the neuromuscular junction; but it antagonizes suxamethonium and potentiates D-tubocurarine.

CLINICAL INVESTIGATIONS OF FLUOTHANE

by DR. T. H. S. BURNS, PROFESSOR W. W. MUSHIN, DR. G. S. W. ORGANE, and DR. J. D. ROBERTSON

The results of clinical trials with fluothane have been reported by Johnstone (1956) and by Bryce-Smith and O'Brien (1956). The Committee has carried out a trial with fluothane in 245 patients undergoing surgical operations in four teaching hospitals.

Methods

The operations are classified in Table VI. There were 118 males and 127 females. The age distribution is shown in Table VII.

Premedication consisted of morphine and atropine or scopolamine in various combinations according to the requirements of the individual patient and to the practice of the anaesthetist concerned. In a few cases atropine only was given, while in two hydrocephalic infants undergoing neurosurgical procedures a small dose of a barbiturate with atropine was used.

Induction with fluothane and air or fluothane and oxygen was employed in 65 patients, the others receiving a sleep dose of thiopentone sodium before the mask was applied to the face. When adequate reflex depression had been achieved orotracheal intubation by direct-vision laryngoscopy was carried out in most of the cases. Thereafter surgical anaesthesia was maintained with fluothane vapour in air, oxygen, or nitrous oxide and oxygen mixture throughout the surgical operation. In 110 cases no muscle relaxant was used. In 123 other cases a small dose of relaxant was

Table VI.—*Classification of Operations*

Operations	No. of Cases	Operations	No. of Cases
Abdominal, upper	21	Lung surgery	7
,, lower	18	Cardiovascular surgery	8
Genito-urinary	12	Other chest operations	5
Orthopaedic	10	Neurosurgery	14
Herniorrhaphy	12	E.N.T.	27
Mastectomy	11	Plastic	17
Thyroidectomy	17	Others	60
Gynaecological	6		245

Table VII.—*Age Distribution*

Age	No. of Cases	Age	No. of Cases
0–9 years	31	50–59 years	40
10–19 ,,	7	60–69 ,,	26
20–29 ,,	38	70–79 ,,	12
30–39 ,,	34	80–89 ,,	5
40–49 ,,	52		245

given before intubation or during the opening or closing of the peritoneal cavity. Usually suxamethonium was employed for this purpose, the average dose being about 50 mg. In 41 cases in the series a competitive blocking type of muscle relaxant was given to see if the cardiovascular effects observed by Johnstone (1956) could be confirmed. Neostigmine sulphate (0.25 mg.), atropine sulphate (0.5 to 1 mg.), and pethidine hydrochloride (up to 50 mg.) were also given in a few cases to observe their effects on the circulation and respiration during fluothane anaesthesia.

In 118 cases fluothane was administered in air or oxygen or nitrous oxide and oxygen from a specially calibrated E.M.O. inhaler (see Appendix B) either for induction and maintenance or during the maintenance of anaesthesia only. Here the concentration of fluothane vapour received by the patient could be accurately determined. On the other hand, in the 137 cases where fluothane was administered from the trichlorethylene bottle of a Boyle apparatus no attempt has been made to assess the fluothane concentration, as it has been shown by Mapleson (see Appendix A) that this varied considerably with small changes in tap setting and temperature. A closed-circuit method was not used in any of the cases referred to in this report in view of the possibility of a rapidly mounting fluothane vapour concentration. A case of fatal cardiac arrest has been reported (Foster, 1957) in which fluothane was used in a closed circuit. The possibility of this being caused by an excessively high fluothane vapour concentration has not been excluded.

In all cases where the peritoneal cavity was opened during the surgical procedure the patient's respiration was assisted or controlled by hand or by a respiratory pump. Otherwise spontaneous respiration was permitted so long as the pulmonary ventilation appeared to be adequate for full oxgenation and carbon dioxide elimination. This allowed observations on tidal exchange and respiratory rate to be made.

The systolic and diastolic blood pressures as measured by a mercury sphygmomanometer, the rate and rhythm of the pulse, the respiratory rate and excursion, and the state of the skin were observed before and at five-minute intervals throughout operation. In addition, in 31 cases the cardiac rhythm was monitored during the period of administration of fluothane and for varying periods after its withdrawal by a continuously recording electrocardiogram. An estimate of blood loss was made by weighing the swabs in 44 cases, and in four patients anaesthetized with fluothane hypotension was induced with a short-acting ganglion-blocking drug "trophenium" (Robertson, Gillies, and Spencer, 1957).

In 10 cases in which major surgical operations were performed under fluothane anaesthesia liver and kidney function has been investigated by a battery of tests on the day before operation, the day after operation, and on one to four subsequent occasions, depending on the findings. In all these cases fluothane vapour in oxygen has been used in known concentrations for induction and maintenance of anaesthesia, and, apart from a small dose of "omnopon" and atropine as premedication, no other sedative, anaesthetic, or relaxant drug has been used. The respiration was assisted as required to ensure adequate pulmonary ventilation throughout. A similar investigation has been carried out in a control series of 10 cases, comparable in respect to pre-operative state, type of operation, surgeon, and premedication. In this group standard anaesthetic techniques have been employed, the anaesthetic agents being sodium thiopentone, nitrous oxide, trichlorethylene, cyclopropane, and ether in various combinations. In addition, in some of these control cases muscle relaxants were used—suxamethonium, gallamine, and D-tubocurarine. Pethidine was used in three cases and trimetaphan in two. The average age of the patients was 57.3 years in the control series and 58.7 years in the fluothane series.

Induction

In approximately 85% of our cases the induction with fluothane was pleasant and rapid, sufficient jaw relaxation and depression of the laryngeal reflexes being present to allow orotracheal intubation in six to seven minutes after commencing the administration. However, on several occasions these conditions were not achieved for up to 13 minutes. In some instances the prolonged induction time occurred in robust subjects, but in many it was associated with marked respiratory depression, so that cyanosis frequently occurred when the fluothane vapour was carried in air. Adding oxygen to the mixture or assisting the breathing by the hand-operated bellows of the E.M.O. inhaler speedily restored the patient's colour to normal in all instances, as the respiratory inadequacy was due to underventilation and not to laryngeal spasm. In most cases where the concentration of fluothane used for induction could be assessed it was between 2 and 3%, the average maximum concentration during induction of anaesthesia being 2.5%.

We were unable to relate the respiratory depression to the type or dose of premedication used, but where the sequence thiopentone sodium–fluothane by E.M.O. inhaler was employed induction tended to be slower than in cases induced with fluothane and oxygen from the Boyle machine. In the former group some depression of breathing was no doubt due to the action of the barbiturate, while in the latter group the concentration of fluothane was uncertain and was probably considerably higher than 2.5%.

Although struggling and coughing were rarely seen, occasionally mild restraint was necessary, especially following the too early insertion of an oral airway.

Circulation During Fluothane Anaesthesia

Blood Pressure

During induction of anaesthesia with fluothane in air or oxygen or nitrous oxide and oxygen the systolic blood pressure often fell considerably, usually to between 80 and 100 mm. Hg. Following the stimulus of endotracheal intubation there was some recovery of pressure, but this rarely lasted for more than a few minutes and by the start of the operation it had frequently fallen again to under 100 mm. Hg. Immediately after the skin incision a slight transitory rise occurred in most cases before it settled down to a steady level, which, in the presence of efficient pulmonary ventilation, was usually maintained throughout the operation. In about 60% of cases this maintenance level of systolic blood pressure was under 100 mm. Hg and in approximately 25% under 80 mm. Hg. In 17 cases the systolic pressure fell to less than 60 mm. Hg. A reduction in the fluothane concentration was usually associated with a rapid recovery of blood pressure. Despite these low pressures the skin remained pink, warm, and dry. We were sometimes struck by the "brick-red colour" of some patients, but spectroscopic analysis of blood samples obtained from a few cases revealed no abnormal blood pigment.

When the ganglion-blocking agent trophenium was administered to four patients anaesthetized with fluothane, a further fall in systolic blood pressure occurred. In each case a steady level of systolic blood pressure between 60 and 70 mm. Hg was maintained throughout the operation by adjusting the intravenous drip rate.

A prompt recovery of the blood pressure occurred in every case after the withdrawal of fluothane, so that by the time the patient was ready to leave the theatre the systolic pressure was usually over 100 mm. Hg.

Heart Rate

There was usually some slowing of the pulse rate within a few minutes of starting the administration of fluothane. In most cases this amounted to 15 to 20 beats a minute, but in a few instances the rate decreased by 50 to 60 beats a minute, pulse rates as low as 40 beats a minute being recorded in a few cases. Following intubation or skin incision there was usually a small rise in pulse rate of 10 to 20 beats a minute, which quickly settled again to a maintenance level of between 80 and 100 beats a minute for the duration of the operation. In approximately 45% of cases the rate remained below 80 beats a minute throughout the administration of fluothane. In a few cases when the pulse rate had fallen to 60 beats a minute or below, the intravenous injection of 0.5 to 1 mg. of atropine sulphate raised the rate by 20 to 30 beats. There was little change in the blood pressure following atropine.

In 45 cases the cardiac rhythm was under electrocardiographic scrutiny during fluothane anaesthesia, and in six of these changes of rhythm were observed. In one hypertensive subject exhibiting inversion to the T wave in the pre-anaesthetic record this became upright during fluothane anaesthesia. Short bursts of ventricular extrasystoles were observed in three patients and two developed auriculo-ventricular nodal rhythm. Towards the end of the operation, in one of these cases in which a shift of the pacemaker had occurred, transient periods of alternating bundle-branch block were observed. Irregularities of the pulse were detected in three other cases during the course of anaesthesia with fluothane in which an electrocardiogram was not taken. Two of these showed bigeminy. In some instances the arrhythmias disappeared spontaneously within a few minutes, but where they persisted a reduction in the concentration of fluothane vapour or the intravenous injection of atropine sulphate, 0.5 to 1 mg., quickly restored the rhythm to normal. On a few occasions where this was done the arrhythmia recurred later in the anaesthesia. There was no clinical evidence of suboxygenation or carbon dioxide retention in any of the cases where alterations in cardiac rhythm were detected.

In most cases bleeding during the operation was reduced, a feature which was favourably commented on by the surgeons. This impression was confirmed by weighing the swabs in 44 cases. The loss was no more than might be expected where hypotension was induced with one of the standard techniques—spinal analgesia or ganglion block.

Respiration During Fluothane Anaesthesia

In the early stages of induction with fluothane in air or oxygen the respirations were deep and regular with little irritation to the airway by the vapour. On the other hand, once consciousness was lost, as has already been mentioned, the breathing became shallow. Where the E.M.O. inhaler was being used with air as the vehicle for the fluothane vapour, cyanosis tended to occur. This reduction in tidal exchange usually persisted during the period of maintenance of anaesthesia with fluothane, some idea of the degree of depression being obtained from the low flow of gases necessary to keep the bellows of the inhaler from collapsing. This reduction in the depth of breathing was usually associated with an increase in rate, 36% of cases showing values of over 30 a minute. In one instance the respiratory rate rose to 60 a minute. Following the intravenous injection of 25 mg. of pethidine a dramatic slowing occurred, respirations dropping within five minutes to 28 a minute. In most cases the breathing tended to be rapid during the first half-hour or so of fluothane anaesthesia and then gradually slowed to between 20 and 30 a minute during the rest of the administration.

Post-operative Period

The laryngeal and swallowing reflexes returned in most cases within a few minutes of stopping the administration of fluothane, so that the patients could safely be returned to bed at the end of the operation. Recovery of consciousness was, however, more variable (see Table VIII).

TABLE VIII

Duration of Fluothane Administration	Recovery Time (Minutes)	
	Range	Average
Less than 29 minutes	15– 60	29·5
30– 59 ,, ...	15– 65	34·5
60–119 ,, ...	25–120	70

In one small infant of 7 months, undergoing a neurosurgical investigation of two hours' duration, consciousness returned five minutes after stopping the fluothane and a feed was offered, taken, and retained (!) within half an hour of return to bed.

Vomiting, although never persistent or distressing, was nevertheless not as rare as preliminary reports have suggested (28%). In fact, the ward sisters were inclined to the view that it was no less than with the usual anaesthetic procedures now employed.

Post-operative chest complications requiring active treatment by the physiotherapist occurred in 4% of the cases. These were all in patients who had had an abdominal operation. Three cases had post-operative wound haematoma and one patient in whom mitral valvotomy was carried out was jaundiced for a few days after operation. This, no doubt, was the result of hepatic congestion associated with a degree of right heart failure. There were seven deaths in the series.

Case 1.—One patient, aged 55, who had had a pneumonectomy, died of pulmonary oedema 36 hours later, after a good initial recovery from the operation.

Case 2.—A man aged 44, who had porto-caval anastomosis under fluothane anaesthesia, died from haemorrhage at a second operation at which fluothane was not used.

Case 3.—A patient with a mediastinal neoplasm died from general cardiovascular failure 14 days after an " orlon " graft had been applied to an innominate vein.

Case 4.—A man of 65 with inoperable carcinoma of the bladder went into congestive heart failure and died 48 hours after bilateral ureteric transplantation. A post-mortem examination revealed a large pulmonary embolism.

Case 5.—A workman fell 40 ft. (12 metres) from a scaffolding and sustained a fracture of the cervical spine and base of the skull as well as a compound fracture of the shaft of one femur. He was unconscious on admission and required intubation to maintain a clear airway. As the level of unconsciousness was less profound on the following morning it was decided to apply skull traction and pin fixation of the fractured femur. A tracheotomy was also carried out to allow aspiration of secretions from the air passages. Light anaesthesia with fluothane and oxygen from a Boyle machine lasting 75 minutes was required to keep the patient immobile during these procedures. Twelve hours later he died, as had been expected.

Case 6.—A man of 46 was admitted with perforation of a gastric ulcer and localized peritonitis. The perforation was closed under fluothane anaesthesia. He developed paralytic ileus in the post-operative period and died on the eleventh day following his operation. At post-mortem examination there was generalized peritonitis, a large right anterior subphrenic abscess, and patchy bronchopneumonic consolidation through the right lung.

Case 7.—A man of 56, with malignant ulcer on the left side of the tongue, received fluothane, nitrous oxide, and oxygen from a Boyle apparatus for a period of 30 minutes for total clearance of remaining teeth and biopsy of tongue ulcer. The immediate post-operative state was satisfactory apart from a rise in temperature to 100.4° F. (38° C.) on the evening of operation. Two days later radium needles were inserted into the tongue under thiopentone, nitrous oxide, and oxygen anaesthesia. His temperature was persistently elevated for the next four weeks. The needles were removed in seven days. Following this he complained of nausea and vomited occasionally. He had an epistaxis which required cautery to the nose. He received 25 mg. of chlorpromazine by intramuscular injection on one occasion. He became relatively afebrile after four days on penicillin and streptomycin followed by a five-day course of chloramphenicol. He was then discharged home. He attended as an out-patient for the application of telecobalt therapy to the neck on three successive days. This treatment was discontinued as he was having attacks of retching. He then developed abdominal pain with small, frequent, loose stools and dark cloudy urine. Four days later he was readmitted to hospital, where he was found to be mildly jaundiced. This rapidly became more marked. He had another epistaxis and gradually became more and more stuporous in the next 48 hours, when he died. At necropsy the liver was very pale and the surface was haemorrhagic. On cutting across it was flabby but not obviously necrotic to the naked eye. The biliary system was normal. Histological examination showed: "A diffuse infiltration of the portal tracts by anaplastic neoplastic cells. There is widespread fatty degeneration of the liver cells and many of the cells are necrotic." Samples of the liver were analysed by Professor Stacey's Department of Chemistry at the University of Birmingham and by the Department of the Government Chemist in London. No significant increase in halogen content was discovered.

The results obtained in the liver- and kidney-function tests carried out in 10 cases anaesthetized with fluothane and in 10 control cases having similar operations under other forms of anaesthesia are briefly summarized in Table IX.

TABLE IX.—*Kidney- and Liver-function Tests Carried Out in* 10 *Cases of Major Surgical Operation Under Fluothane and* 10 *Controls*

Test	Series	No Deterioration in Function Detected	Definite Deterioration Detected	Doubtful Deterioration Detected	Deterioration May be Due to Anaesthetic
Kidney function	Control (10)	7	3	0	3
	Fluothane (10)	5	5	0	4
Liver function	Control (10)	3	6	1	6
	Fluothane (10)	5	4	1	4

Kidney-Function Tests:—Routine urine examination: urine volume, albumen, sugar, acetone, bile salts and pigments; creatinine clearance; urea clearance.

Liver-Function Tests:—Prothrombin time and activity; serum bilirubin; alkaline phosphatase; cephalin cholesterol flocculation; thymol turbidity and flocculation; bromosulphthalein excretion; electrophoresis of serum proteins.

Discussion

Induction

As an induction agent fluothane resembles the anaesthetic gases, nitrous oxide and cyclopropane, more than the volatile liquids, ether, ethyl chloride, and trichlorethylene, in its respirability, lack of secretion formation, and rapidity of action. In these respects also it merits comparison with chloroform, a drug which has now been largely abandoned as an induction agent because of the occasional death from sudden cardiac failure. The exact mechanism responsible for these syncopes in early chloroform anaesthesia is still the subject of speculation, but it seems probable that they may be of two types—vagal inhibition and ventricular fibrillation. From our observations with fluothane it would seem that a considerable degree of inhibition occurs frequently during induction, the pulse slowing in many cases to between 50 and 60 beats a minute and in a few to 40 beats a minute. However, with an adequate dose of atropine the danger of cardiac arrest from this mechanism should be absent; this dosage would have to be higher than that usually employed in premedication—for example, 2 mg. for an adult patient. Ventricular extrasystoles have been observed both by Johnstone (1956) and by us during fluothane anaesthesia, but in no instance have these occurred during the period of induction nor have they been of the multifocal variety usually considered to be the precursors of ventricular fibrillation.

On the other hand, the marked depression of respiration with associated risk of suboxygenation and carbon dioxide retention are potentially capable of precipitating this form of arrhythmia. Further, Raventós (1956) observed that the sensitivity of the heart was increased when adrenaline was injected intravenously in dogs. He stated, however, that he was able to inject up to 200 ml. of 1 in 100,000 adrenaline subcutaneously in the same animal without producing disturbances of heart rate or rhythm, and we observed no clinical evidence of irregularity of the pulse in two cases in which the neck was infiltrated with a solution of 30 ml. and 50 ml. respectively of 0.5% procaine hydrochloride containing 1 in 200,000 adrenaline hydrochloride solution nor in 25 cases in which 10–40 ml. of 1 in 500,000 noradrenaline in saline solution was infiltrated into the operation site. Thus, although fluothane looks disturbingly similar to chloroform in many respects, properly managed, the danger of primary cardiac syncope may be very much less during induction of anaesthesia with fluothane.

In discussing the induction of anaesthesia it is impossible to avoid comparison of fluothane with drugs, particularly barbiturates, which are given intravenously for this purpose. Thus, while fluothane may be favourably compared with the inhalation anaesthetics as an induction agent, the speed and pleasantness of action and the ease of administration have made intravenous sodium thiopentone the most popular agent with both patients and anaesthetists for induction of anaesthesia—a position which it would be difficult for any type of inhalation anaesthetic to challenge at the present time. The popularity of the intravenous route for inducing anaesthesia has been made doubly secure since the introduction of the short-acting muscle relaxants which have reduced the danger of laryngeal spasm associated with endotracheal intubation under sodium thiopentone. On the other hand, in that group of cases where inhalation anaesthetics are still frequently preferred for induction—namely, cases of intestinal obstruction, and frail, elderly, and shocked patients—the marked falls in blood pressure which have been observed in many cases induced with fluothane would suggest that it was a less suitable agent than nitrous oxide or cyclopropane in the poor-risk patients.

Maintenance

Once surgical anaesthesia has been achieved a concentration of 1 to 1.5% of fluothane vapour in air or oxygen was usually sufficient to maintain a steady level of anaesthesia. As we have already mentioned, the average maintenance level of arterial blood pressure in the majority of cases was much lower than during anaesthesia with other commonly employed general anaesthetic agents. Variations in the pressure level paralleled closely the concentration of fluothane which was being inhaled. When the level of anaesthesia was unduly light, various surgical stimuli, such as incision of the skin or traction on the mesentery, were associated with a transient rise or fall of blood pressure. This usually returned promptly to the previous level when the stimulus was withdrawn, but it was taken as an indication to deepen the level of anaesthesia. A rapid recovery of blood pressure occurred in most cases when the fluothane administration was stopped at the end of the operation. In a few instances where the subnormal level persisted it is possible that the replacement of blood lost during the operation had been inadequate.

It has been stated in previous reports that bleeding from the wound at operation is less during fluothane anaesthesia than that usually encountered with other forms of anaesthesia. Presumably this reduction of bleeding is a function of the lower average level of systemic blood pressure which exists during fluothane administration, so that a reduction in surgical blood loss is hardly surprising. Intentionally induced hypotension is now widely employed to reduce bleeding at operations so that the subnormal blood-pressure level observed during fluothane anaesthesia is not *per se* an unattractive feature. It is, however, important that we should have a clear knowledge of the mechanism responsible for the reduction in blood pressure, for upon this depend the safety and controllability of the method. It has now been generally accepted that a block of conduction in the autonomic ganglia with consequent peripheral vasodilatation is the safest and most satisfactory way at present available.

Other methods, such as arteriotomy and direct depression of contractility of the heart with anaesthetics, are associated with compensatory vasoconstriction, so that there is a danger that tissue anoxia may be produced. Although Raventós (1956) has claimed from experiments in cats and dogs that the cardiac output was not altered and that vasodilatation in the splanchnic area, probably due to a sympathetic ganglion block, is the main cause of hypotension during anaesthesia with fluothane, the evidence cited in the pharmacological section of this report suggests strongly that this is not the only factor involved. There is then some reason to suspect that the fall in blood pressure produced by fluothane may be more dangerous than hypotension of a similar degree caused by drugs which act solely on the autonomic ganglia.

The concentration of fluothane inhaled appeared to be the main factor affecting the pulse rate as it was with the blood pressure.. On the other hand, in a few cases the pulse rate tended to remain at about the pre-anaesthetic level throughout the operation, although the blood pressure had fallen considerably. Further, in those cases that had had gallamine triethiodide the pulse rate rose while the blood pressure showed a reduced but still significant degree of depression. This would suggest that the two effects are to some extent at least independent of one another. The fact that a rise in pulse rate occurs following the administration of atropine sulphate or gallamine triethiodide at any time during the administration of fluothane shows that vagal restraint remains active even during prolonged anaesthesia.

In view of the small number of cases in the series in which electrocardiographic monitoring was carried out during the entire period of fluothane administration, it would be misleading to attempt to analyse either the frequency or significance of arrhythmia during fluothane anaesthesia. The electrocardiogram has, however, confirmed the suspicion that most of the irregularities observed are in fact ventricular extrasystoles. In some of these cases the arrhythmia seemed to be related to the concentration of fluothane being administered, a reduction generally being followed by its disappearance. On the other hand, in several instances the rhythm returned to normal within a few minutes without any change in concentration of composition of the inhaled gases being made. Johnstone (1956) states that in each of the 12 cases in his series in which ventricular extrasystoles were observed they were associated with respiratory depression, and that in each case they were quickly abolished by assisting the respiration. We have not observed an association of this sort, though it is likely that carbon dioxide retention and oxygen deficiency can play an important part in the production of arrhythmias during general anaesthesia. In no case in our series has there been electrocardiographic evidence which by itself would be sufficient to indicate myocardial damage. While alternating bundle-branch block as an isolated finding would not itself constitute evidence of myocardial damage, it does indicate an impairment of conduction which, if sufficiently prolonged, could produce Stokes–Adams syncope.

Muscle Relaxants

After induction of anaesthesia with a small dose of sodium thiopentone, a single dose of suxamethonium chloride or gallamine triethiodide was used to facilitate endotracheal intubation in approximately half of the cases in the series. Otherwise the specific muscle relaxant agents were used only in a minority of the cases. There were several reasons for this. In the first place, we were anxious to assess the ability of fluothane to produce muscular relaxation at various levels of anaesthesia. Secondly, in 10 cases liver- and kidney-function tests were being carried out and it was important to avoid the use of any other drugs which might complicate the results. Thirdly, in view of the alarming falls in blood pressure and circulatory collapse reported by Johnstone (1956) after the intravenous injection of 15 mg. of D-tubocurarine chloride, its accentuation by positive-pressure inflation of the lungs and the administration of 0.5 mg. of atropine followed by 2.5 mg. of neostigmine, we felt that the competitive type of muscle relaxant drug should be used with great caution in association with fluothane anaesthesia. This has received support from the evidence given elsewhere in this report that fluothane potentiated the ganglion-blocking action of D-tubocurarine chloride.

In those cases where muscular relaxation was produced with fluothane alone reasonable operating conditions were obtained even for operations on the stomach and gallbladder. There is no doubt, however, that the level of anaesthesia required was much deeper than would have been necessary if a specific muscle relaxant drug had also been used. For this reason the blood-pressure level throughout these operations was unduly low. Further, as has been reported by Bryce-Smith and O'Brien (1956), pulmonary ventilation was depressed during fluothane anaesthesia, especially if the level was sufficient to allow intra-abdominal surgery. It was therefore considered necessary to assist or control the breathing in a large number of our cases.

In 41 cases in this series D-tubocurarine chloride, gallamine triethiodide, or suxamethonium chloride has been given during the maintenance period of fluothane anaesthesia. In none of these cases has an alarming fall in arterial blood pressure occurred which might be related to the relaxant drug. This may, in part at least, be due to the fact that, for the reasons already given, the amount of these drugs administered was smaller than we are accustomed to employ, the average individual doses being 5–10 mg., 40–80 mg., and 30–60 mg. respectively of D-tubocurarine, gallamine, and suxamethonium. In one patient to whom atropine sulphate, 0.75 mg., followed by neostigmine sulphate, 2.5 mg., was given intravenously at the end of operation to counteract the residual effect of D-tubocurarine, the systolic blood pressure fell from 120 to 80 mg. Hg and the pulse rate slowed by 30 beats a minute. Both pulse and blood pressure recovered slowly over the next quarter of an hour as the respiratory minute volume improved.

Post-operative Period

Two of the principal claims for fluothane have been the speed of recovery of consciousness and the rarity of vomiting following even prolonged anaesthesia with this agent. In neither respect have we been particularly impressed in comparison with the results commonly observed with other modern anaesthetic agents and techniques. Thus, although the initial recovery was rapid, the laryngeal and swallowing reflexes returning usually within a few minutes of withdrawal of the fluothane, the recovery of consciousness appeared to bear a definite relation to the duration and depth of the fluothane anaesthesia. Although vomiting was rarely a distressing feature, and certainly not comparable to that following prolonged ether anaesthesia, nevertheless the incidence was not appreciably less than with other commonly used anaesthetic agents. In fact, we found that when the ward sisters were unaware of the type of anaesthetic used they could not distinguish the patients to whom fluothane had been given.

Liver and Kidney Function

Raventós (1956) carried out two tests of renal and two of hepatic function in several rats and dogs following repeated periods of anaesthesia with fluothane. No significant difference was found between the results of the control tests and those carried out after anaesthesia. None of these cases was subjected to any operative procedure. On the other hand, sections of specimens from these animals revealed dilatation of the proximal convoluted tubules of the kidneys associated with slight cytological changes in the cells of these tubules. He also reports "minor" but unspecified histopathological changes in the livers. Comparison with the changes produced in liver and kidneys of mice by chloroform is hardly relevant, as chloroform is now rarely used alone as an anaesthetic agent in major surgery in humans.

The striking feature about the results of our studies of liver and kidney function in both the fluothane and the control series is the considerable proportion of cases in which evidence of deterioration of function in one or both organs occurred after operation. Although the anaesthetic agent cannot be excluded as a factor leading to this impairment of function in the post-operative period, there are many other factors connected with a surgical operation which are known to affect the activity of the liver and kidneys. Thus protein catabolism, starvation, dehydration, blood transfusion, absorption of extravasated blood, and alterations in organ blood flow are common to most operations and particularly to those within the abdomen. In addition, minor variations in the technique of collection of specimens or in the biochemical estimations and variable factors connected with the anaesthetic management, such as anoxia, falls in systemic blood pressure, etc., may to some extent account for alterations in the results over the period of study. So far as possible such confusing factors have been avoided in this investigation, but in every case in which deterioration of liver or kidney function was observed several of these were known to be involved.

Further, wherever clinical evidence of impaired function was seen following operation this had either been present in some degree before operation or some obvious cause, such as urinary retention, was present to account for it. It should also be emphasized that many of the patients in this investigation could be classed as " poor surgical risks " who were undergoing extensive procedures involving a considerable degree of tissue damage, metabolic upset, blood and fluid loss, and restriction of fluid intake. Thus, despite the high incidence of deterioration in liver and kidney function observed in this investigation, it is doubtful whether in any single case the anaesthetic agent can be held responsible. The fact that impairment occurred with approximately equal frequency in the control and in the fluothane series suggests that, even if the anaesthetic is a factor, it is unlikely that fluothane is significantly worse in this respect than the other anaesthetics used. Before any definite conclusions could be reached, either a very much larger series would require to be studied or variations in liver and kidney function would have to be observed in a number of subjects anaesthetized with fluothane and with other anaesthetic agents, but not subjected to operation.

GENERAL DISCUSSION

Pharmacological and clinical experience with fluothane agrees remarkably well in several respects. First, both in animals and in man hypotension is produced. The hypotension in man is marked by the retention of a warm pink skin, and by a modest reduction in bleeding during surgical operation ; the analogies with hypotension by ganglion block or spinal analgesia are clear. Likewise in the cat, the fall in blood pressure is not accompanied by any signs of sympatho-adrenal discharge, and yields a steady blood-pressure tracing resembling that of the spinal pithed animal more than any other. But neither in man nor in the cat can a general ganglion block by fluothane be plausibly postulated ; and the evidence suggests that the hypotension is due to a depression of central vasomotor centres combined with diminished cardiac output.

Secondly, transmission through the vagal ganglia is remarkably unimpaired by the anaesthetic. Although in the cat anaesthetized with chloralose no marked bradycardia occurs, it can be striking in man, and is abolished by suitable dosage with atropine.

Thirdly, in the cat, fluothane can potentiate the ganglion-blocking action of drugs such as hexamethonium or D-tubocurarine. With the latter, ganglion-block is probably not usually of major clinical importance ; but under fluothane it would be expected to become significant. It may be that this accounts for Johnstone's experience clinically, in which he found serious hypotension to follow the use of D-tubocurarine during fluothane anaesthesia. If the possibility of ganglion block is not appreciated, it would be easily possible, by overventilation or by slight postural change, to produce an unexpected hypotension.

Fourthly, the animal and clinical experience described in this report agree in finding that recovery from the anaesthesia is not always as rapid as predicted from earlier reports, although in the blood pressure at least there is regularly a rather prompt *partial* recovery. Further information about the distribution and elimination of fluothane is needed.

Despite our advance in knowledge about fluothane, a final opinion cannot be passed on it at the present stage. Only when several thousand patients have been anaesthetized with it will it become possible to estimate its advantages and disadvantages with accuracy.

Provisionally, it may be said that the properties of fluothane indicate that there is a good hope of finding a safe and pleasant inhalation anaesthetic which is not explosive. Fluothane is an important step in that direction and can provide a flexible and effective anaesthesia. It appears, however, not to be as pleasant as cyclopropane and not to be as safe as ether. It is clear that fluothane should not be administered by an untrained person, because it depresses respiration and may even arrest it during the early stages of administration, and because it depresses the blood pressure. The possible dangers of assisted respiration with a potent drug in the closed circuit have been mentioned. Even in the hands of a skilled anaesthetist wishing to use an anaesthetic given by inhalation, there are certain patients for whom ether or cyclopropane is preferable. For the time being, therefore, the advent of fluothane does not remove the necessity for taking precautions against electrostatic charge and other electrical hazards of operating-theatre equipment.

APPENDIX A

REPORT ON CALIBRATION, FOR FLUOTHANE, OF TRILENE VAPORIZING UNIT OF THE BRITISH OXYGEN GASES LTD., BOYLE-TYPE ANAESTHETIC APPARATUS

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The fluothane concentration emerging from the Boyle apparatus was determined by passing oxygen through it and drawing a sample, at the outlet, through a katharometer. The katharometer was calibrated by a mixture of fluothane in oxygen, saturated at a known temperature.

The main factors which affect the emergent concentration of fluothane are : (1) gas flow ; (2) distance from plunger to fluothane surface ; (3) temperature of fluothane ; and (4) tap setting. The factor of varying eccentricity of plunger and U-tube was eliminated in all units calibrated by adopting the Hillard (1957) modification.

1. In these calibrations the gas flow was kept constant at 7 litres a minute.

2. It was found that, although the concentration generally decreased as the plunger-to-surface distance increased, there was a tendency to a " flat " in the characteristic. Thus a suitable setting of the plunger, different for different units, could be selected, so that a fall in liquid level from the 24- to the 16-drachm mark had very little effect on the concentration. (This represents about one hour's use at 1½% fluothane.) Outside this range the concentration may fall by as much as one-third for an evaporation of 8 dr. (28 ml.). By requiring that the liquid level be maintained between 24 and 16 dr. (84 and 56 ml.), and by fixing the plunger in the appropriate position, a calibration could be prepared in terms of tap setting and fluothane temperature.

3. The effect of fluothane temperature on concentration is considerable: a fall from 25 to 15° C. (which is not uncommon in clinical usage) reduces the concentration by one-third (see calibration graph, Fig. 10).

4. Small changes in tap setting gave large changes in concentration: a movement of 1 or 2 mm. was sufficient to change the concentration by ½ to 1% fluothane. In the old style tap, manufactured before January 1, 1947, the effect was so marked that units incorporating these taps were rejected. Variation between individual taps necessitated the individual calibration of each vaporizing unit.

Since making these calibrations Falkner Hill (1957) has published some measurements made on a modified trilene unit. The concentrations he obtained were somewhat lower than those shown in Fig. 10, but the discrepancies could well be due to the different conditions.

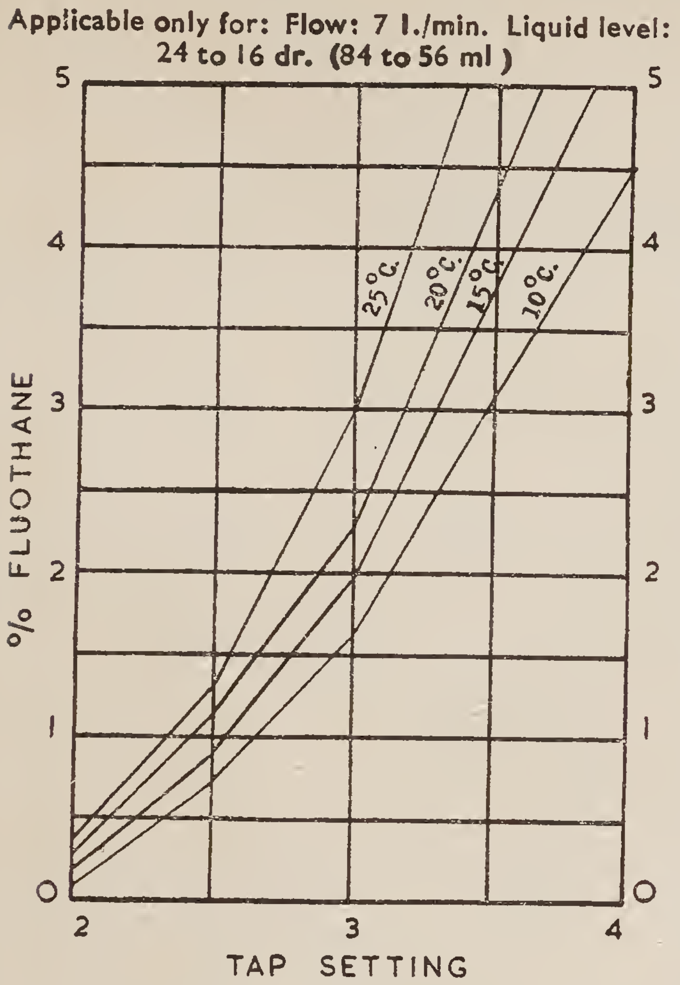

FIG. 11.—Typical calibration of one vaporizing unit for four temperatures of the liquid fluothane. The tap-setting numbers refer to the four horizontal lines, alongside the lever, which separate the words "off" and "on." The lines are spaced at approximately 1-cm. intervals.

APPENDIX B

INHALERS USED IN TRIALS FOR ADMINISTERING MIXTURES OF FLUOTHANE VAPOUR WITH AIR OR WITH MEDICAL GASES

BY

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The inhalers used both for clinical and for pharmacological trials were based on the apparatus (E.M.O.) developed in recent years for ether anaesthesia (Epstein and Macintosh, 1956). These possess a concentration scale calibrated up to 20% ether vapour, and a temperature compensator which ensures that within a range of from 60 to 85° F. (15.5 to 29.4° C.) the concentrations remain fairly constant. The ether concentrations delivered vary only slightly for respiratory minute volumes from 7 to 12 litres.

The original plan of using these standard inhalers with only slightly modified concentration control and thermo-compensator had to be abandoned when the particular chemical properties of fluothane became better known. A prototype inhaler used with fluothane since October, 1955, showed progressive corrosion of certain parts. Some months later it had become obvious (*a*) that fluothane vapour in the presence of atmospheric air strongly corrodes light metal alloys as well as tin; and (*b*) that most of the common, resilient gasket materials made from artificial rubber and other elastomers are attacked to varying degrees.

Various protective methods were tried in the inhalers used for the trials. In the latest models corrosive attack has been excluded by covering all exposed metal parts with a nylon layer and by using gaskets made from similar materials.

Fluothane which had been kept in one of these inhalers which was in regular use for two months in the trials was examined by Professor Stacey's department. Gas chromatography, infra-red spectroscopy, and chemical analysis showed it to be indistinguishable from the contents of a fresh bottle of fluothane supplied by the manufacturers.

Inhalers for Clinical Trials

Concentration Range.—The concentration control was modified to permit administration of vapour up to 3 or 4% (v./v.) in some of the inhalers. Preliminary investigations on animals had shown that the maximum concentrations required in clinical work was unlikely to exceed these values.

Temperature Control.—In order to avoid further delays, no attempt was made to adapt the temperature compensator for a wide range of ambient temperatures. It was considered adequate to limit accurate regulation of concentrations to a range of from 65 to 75° F. (18.5 to 24° C.). Actually the regulation was quite satisfactory for clinical work even outside this range. Thus, for a fixed minute volume the variation in concentration with the control set to the 2% mark was less than 0.1% (v./v.) when the temperature rose from 63 to 85° F. (17 to 29.4° C.).

Calibration.—The concentrations delivered at varying temperatures and flow rates were measured by means of a gas refractometer. Intermittent flows of air between 5 and 10 litres a minute, simulating the patient's respiration, were passed through the inhaler and samples of the output were analysed continuously. The absolute concentration values were based on calibration of the analyser with known fluothane/air mixtures and also on published values for the refractive index (I.C.I., 1956).

Effect of Respiration.—The vapour density of fluothane is approximately two and a half times that of ether, and without special modifications of the ducts in the inhaler an increased variation of concentration with respiratory minute volume was to be expected. Nevertheless, for minute volumes down to 6 litres the concentrations decrease only slightly. An inhaler delivering 2.8% (v./v.) at 9 litres a minute (22 respirations a minute), gave an output of 2.6% at 6 litres a minute. The concentration decreased to 2.1% at 5 litres a minute and to 1.9% at 4 litres a minute. For a lower setting of the concentration control the variations in vapour strength are less pronounced.

Use of Inhaler.—In view of the very low respiratory exchange which may occur during fluothane anaesthesia, certain rules should be observed to ensure that the strength of mixture delivered to the patient is known with reasonable accuracy. (*a*) When the apparatus is used as a draw-over inhaler for fluothane/air mixtures, the bellows unit containing the non-return valves is inserted between inhaler and patient.* As mentioned above, the vapour strength would decrease appreciably if the respiration fell to 5 litres a minute or below. Repeated manual depressions of the bellows followed by their unimpeded expansion will flush the system with the correct mixture so that the inhaled concentration is again near that indicated by the concentration control. (*b*) If medical gases are to be given with fluothane vapour, the inhaler should be inserted between the bellows unit and the patient. The medical gases are best admitted to the main inlet of the bellows unit, whereby inadvertent dilution with air is avoided. This arrangement permits also an approximate estimation of the respiratory minute volume, by adjusting the metered gas flow until the bellows oscillate about their normal position. There is another advantage in adjusting the gas flow to the patient's requirements: if the flow should greatly exceed the respiratory requirements, the vapour strength delivered would deviate from the indications on the concentration scale; the present procedure considerably reduces such variations.

Inhalers for Pharmacological Investigations

Most of the apparatus for the pharmacological investigations with fluothane, trichlorethylene, and chloroform were based on the standard E.M.O. inhaler. In order to ensure uniformity, it was decided to draw the vapour/air mixtures from the inhaler with Starling's respiration pump, readily available at the various centres.† This pump has an extremely rapid "inspiratory" phase: owing to this characteristic feature, the concentration obtained from inhalers built for human respiration was fairly high, although the ventilation was never above 4 litres a minute, and usually only 2 litres a minute.

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*See brochure supplied by Pentland Instrument Co. Ltd.

In most of the experiments no spontaneous respiration was present; the lungs were inflated by the pump which "inspired" the vapour/air mixture from the inhaler. When the animal was breathing spontaneously the pump was used to keep reservoir bags made from "polythene" film filled with the required mixture. In the latter arrangement low resistance non-return and expiratory valves were used between reservoir bag and animal, which was usually intubated with a cuffed endotracheal tube.

The inhalers were calibrated similarly to those used in the clinical trials. The ventilation rate of the pump was varied between 19 and 26 a minute; the stroke volumes were chosen between 50 ml. and 200 ml. For this range the vapour strength depends mainly on the minute volume (stroke × rate) and appropriate calibration charts were worked out. Actually the change in concentration for certain control positions was quite small when the minute volume was increased by 50%; thus at 1.6 vol.% there was practically no change, while an initial output of 2.2% (v./v.) was raised to 2.6% (v./v.) by this increase in minute volume.

The inhalers were equipped with thermocompensators, but in order to ensure a high degree of accuracy all calibrations were carried out by immersing the inhaler in a thermostat bath kept at 70° F. (21° C.).

If the inhalers were used normally with varying ambient temperatures, there was a slight decrease in concentration with rising temperature.

An output of 1.50% (v./v.) at 60° F. (15.5° C.) decreased to 1.32% when the temperature rose to 72° F. (22.2° C.). Similar variations occurred for other positions of the concentration control.

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